# United States Patent Application for:

## Aerosolization Apparatus with Non-Circular Aerosolization Chamber


Inventors:

1) William Alston
a citizen of United States of America;
2336 Westmoreland Drive
San Jose, CA 95124;

2) Jeff R. Wood
a citizen of United States of America;
1872 Appletree Lane
Mountain View, CA 94040;

3) John F. Burr
a citizen of United States of America;
11350 Cedarwood Way
Redwood City, CA 94061.

4) Mark J. Glusker
a citizen of United States of America;
128 Avila Road
San Mateo, CA 94402.



Assignee: Nektar Therapeutics
(formerly Inhale Therapeutic Systems, Inc.)
150 Industrial Road
San Carlos, CA 94070

Entity: Large Entity

Docket No.: 0175.00


CERTIFICATE OF EXPRESS MAILING:

"Express Mail" mailing label number ER212309829US Date of Deposit _____

I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Box Patent Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

_____
Name of Person Mailing Paper

Signature of Person Mailing Paper

# Aerosolization Apparatus with Non-Circular Aerosolization Chamber

This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/435,966, filed on December 19, 2002, which is incorporated herein by reference in its entirety.

## BACKGROUND

The need for effective therapeutic treatment of patients has resulted in the development of a variety of pharmaceutical formulation delivery techniques. One traditional technique involves the oral delivery of a pharmaceutical formulation in the form of a pill, capsule, elixir, or the like. However, oral delivery can in some cases be undesirable. For example, many pharmaceutical formulations may be degraded in the digestive tract before they can be effectively absorbed by the body. Inhaleable drug delivery, where an aerosolized pharmaceutical formulation is orally or nasally inhaled by a patient to deliver the formulation to the patient's respiratory tract, has proven to be a particularly effective and/or desirable alternative. For example, in one inhalation technique, an aerosolized pharmaceutical formulation provides local therapeutic relief to a portion of the respiratory tract, such as the lungs, to treat diseases such as asthma, emphysema, and cystic fibrosis. In another inhalation technique, a pharmaceutical formulation is delivered deep within a patient's lungs where it may be absorbed into the blood stream. Many types of inhalation devices exist including devices that aerosolize a dry powder pharmaceutical formulation.

One type of inhalation device aerosolizes a pharmaceutical formulation that is stored in a capsule. For example, a dose or a portion of a dose of a dry powder pharmaceutical formulation may be stored in a capsule, and the capsule may be inserted into an aerosolization device which is capable of aerosolizing the pharmaceutical formulation. The aerosolization may be accomplished by causing the capsule to move within a chamber, for example by flowing air through the chamber using a user's inhalation pressure to generate the airflow. As the capsule moves within the chamber, the pharmaceutical formulation exits the capsule though one or more openings in the capsule, and the pharmaceutical formulation is entrained by the flowing air in an aerosolized form. The aerosolized pharmaceutical formulation may then be inhaled by the user,

and a dose or portion of a dose of the aerosolized pharmaceutical formulation may be delivered to the user's respiratory tract.

The size and quality of the dose delivered to the user is dependent on the amount and condition of aerosolizable pharmaceutical formulation that exits the capsule. However, in conventional aerosolization devices, the amount and condition of the aerosolizable pharmaceutical formulation may vary from use to use and/or from user to user. For example, sometimes it is difficult to cause large amounts of the pharmaceutical formulation to exit the capsule when a user is unable to generate a high flow rate inhalation. In addition, it is sometimes difficult to cause large amounts of the pharmaceutical formulation to exit the capsule during very high flow rate inhalations due to compaction of the pharmaceutical formulation within the capsule. The inefficient release of pharmaceutical formulation can be costly and can result in the necessity for numerous operations of the device in order to achieve a desire dosage. In some circumstances, the pharmaceutical formulation exits the capsule in agglomerated form, the agglomerations being undesirably large for inhalation therapy.

Therefore, it is desirable to be able to aerosolize a pharmaceutical formulation in a consistent manner. It is further desirable to be able to aerosolize a pharmaceutical formulation in a manner that extracts an increased amount of the pharmaceutical formulation from a receptacle. It is also desirable to be able to aerosolize a pharmaceutical formulation in a more deagglomerated form.

## SUMMARY

The present invention satisfies these needs. In one aspect of the invention, an aerosolization apparatus comprises a chamber that receives a receptacle, and the chamber has a non-circular cross section.

In another aspect of the invention, an aerosolization apparatus comprises a body defining a chamber having an air inlet and an air outlet, wherein the chamber is sized to receive a receptacle containing a pharmaceutical formulation in a manner which allows the receptacle to

move within the chamber; wherein the chamber comprises a longitudinal axis which is substantially parallel to an inhalation direction and wherein the chamber has a cross-section orthogonal to its longitudinal axis that is non-circular, whereby when a user inhales, air enters into the chamber through the inlet to cause the receptacle to move within the chamber so that the pharmaceutical formulation exits through an opening in the receptacle and is aerosolized for delivery to the user through the outlet.

In another aspect of the invention, an aerosolization apparatus comprises a body defining a chamber having an air inlet and an air outlet, wherein the chamber is sized to receive a receptacle containing a pharmaceutical formulation in a manner which allows the receptacle to move within the chamber; wherein the chamber comprises a longitudinal axis which is substantially parallel to an axis passing centrally through the outlet and wherein the chamber has a cross-section orthogonal to its longitudinal axis that is non-circular, whereby when a user inhales, air enters into the chamber through the inlet to cause the receptacle to move within the chamber so that the pharmaceutical formulation exits through an opening in the receptacle and is aerosolized for delivery to the user through the outlet.

In another aspect of the invention, an aerosolization apparatus comprises a body defining a chamber having an air inlet and an air outlet, wherein the chamber is sized to receive a receptacle containing a pharmaceutical formulation in a manner which allows the receptacle to move within the chamber; wherein the chamber comprises a longitudinal axis which is substantially perpendicular to an inhalation direction and wherein the chamber has a cross-section along a plane parallel to its longitudinal axis, the cross-section being non-circular, whereby when a user inhales, air enters into the chamber through the inlet to cause the receptacle to move within the chamber so that the pharmaceutical formulation exits through an opening in the receptacle and is aerosolized for delivery to the user through the outlet.

In another aspect of the invention, a method of aerosolizing a pharmaceutical formulation comprises providing a receptacle containing a pharmaceutical formulation; inserting the receptacle into a chamber having a non-circular cross section; and inhaling through an opening in the housing to cause air to flow into the chamber thereby causing the receptacle to move about

the non-circular cross section to aerosolize the pharmaceutical formulation.

## DRAWINGS

These features, aspects, and advantages of the present invention will become better understood with regard to the following description, appended claims, and accompanying drawings which illustrate exemplary features of the invention. However, it is to be understood that each of the features can be used in the invention in general, not merely in the context of the particular drawings, and the invention includes any combination of these features, where:

Figure 1A is a schematic sectional side view of a version of an aerosolization apparatus according to the invention in an initial position;

Figure 1B is a schematic sectional side view of the version of an aerosolization apparatus shown in Figure 1A at the beginning of an aerosolization process;

Figure 1C is a schematic sectional side view of the version of an aerosolization apparatus shown in Figure 1A during an aerosolization process;

Figures 2A and 2B are schematic sectional end views of a version of an aerosolization apparatus having a non-circular cross section chamber;

Figures 3A through 3H are schematic sectional end views of a other versions of an aerosolization apparatus having a non-circular cross section chamber;

Figure 4A is a schematic sectional side view of a version of an aerosolization apparatus in a rest position;

Figure 4B is a schematic sectional side view of the version of an aerosolization apparatus shown in Figure 4A just before capsule puncture;

Figure 4C is a schematic sectional side view of the version of an aerosolization apparatus shown in Figure 4A as the capsule is being punctured;

Figure 4D is a schematic sectional side view of the version of an aerosolization apparatus shown in Figure 4A just after capsule puncture; and

Figure 4E is a schematic sectional side view of the version of an aerosolization apparatus shown in Figure 4A in use.

## DESCRIPTION

The present invention relates to an aerosolization apparatus. In particular, the invention relates to an aerosolization apparatus capable of aerosolizing a pharmaceutical formulation contained in a receptacle, such as a capsule. Although the process is illustrated in the context of aerosolizing a dry powder pharmaceutical formulation for inhalation, the present invention can be used in other processes and should not be limited to the examples provided herein.

An aerosolization apparatus **100** according to the present invention is shown schematically in Figure 1A. The aerosolization apparatus **100** comprises a housing **105** defining a chamber **110** having one or more air inlets **115** and one or more air outlets **120**. The chamber **110** is sized to receive a receptacle **125** which contains an aerosolizable pharmaceutical formulation. The receptacle **125** has an opening **130** thereinto that provides a communication between the chamber **110** and the pharmaceutical formulation within the receptacle **125**. Near or adjacent the outlet **120** is an end section **140** that may be sized and shaped to be received in a user's mouth or nose so that the user may inhale through an opening **145** in the end section **140** that is in communication with the chamber outlet **120**.

The aerosolization apparatus **100** utilizes air flowing through the chamber **110** to aerosolize the pharmaceutical formulation in the receptacle **125**. For example, Figures 1A through

1C illustrate the operation of a version of an aerosolization apparatus **100** where air flowing through the inlet **115** is used to cause aerosolization of the pharmaceutical formulation and the aerosolized pharmaceutical formulation flows through the outlet **120** so that it may be delivered to the user through the opening **145** in the end section **140**. The aerosolization apparatus **100** is shown in its initial condition in Figure 1A. The receptacle **125** is positioned within the chamber **110** and the pharmaceutical formulation is secured within the receptacle **125**. In the version shown, a partition **150** blocks the forward end of the chamber **110**, and the partition **150** has the one or more outlets **120** extending therethrough.

Air or other gas is then caused to flow through an inlet **115**, as shown by arrows **155** in Figure 1B. For example, the airflow **155** may be generated by a user inhaling **160** through the opening **145** in the end section **140**. The airflow **155** initially draws the receptacle toward the partition **150**. Continued airflow **155**, as shown in Figure 1C, causes the receptacle **125** to move within the chamber **110**. In the configuration shown, the receptacle **125** may contact the partition **150** at its forward end and then move about the sidewall **165** of the capsule with its rearward end contacting the sidewall **165**. For example, the rearward end of the receptacle **125** may rotate and/or slide around the sidewall **165** of the chamber **110**. This movement causes the pharmaceutical formulation in the receptacle **125** to exit through the opening **130** and become aerosolized in the airflow **155**. The aerosolized pharmaceutical formulation is then delivered to the user's respiratory tract during the user's inhalation **160**. In another version, compressed air or other gas may be ejected into an inlet **115** to cause the aerosolizing air flow **155**, and the aerosolized pharmaceutical formulation is then inhaled by the user.

The pharmaceutical formulation may be more efficiently and/or more effectively aerosolized by providing the sidewall **165** of the chamber **110** with a non-circular cross section **170** that contacts the receptacle **125** as the receptacle **125** rotates and/or slides around the sidewall **165**. A version of a non-circular cross section **270** is shown in Figures 2A and 2B. In this version, the non-circular cross section is provided by one or more projections **175** that extend lengthwise along the sidewalls **165** of the chamber **110**. Figure 2A shows the receptacle **125** as it rotates and/or slides along the sidewall **165**. When the receptacle **125** encounters a projection **175**, as shown in Figure 2B, the receptacle **125** is bounced or jarred or otherwise disturbed. As a result, the

pharmaceutical formulation within the receptacle **125** is also disturbed and the aerosolization is improved. For example, at low flow rates, the disturbance is sufficient to cause an increased amount of the pharmaceutical formulation to be caused to exit through the opening **130**. In addition, it has been determined that at high flow rates, some of the pharmaceutical formulation agglomerates along the inner wall of the receptacle **125** and is difficult to aerosolize. However, the non-circular cross section **170**, such as the projection **175**, serves to break up the agglomerations and allows for a greater amount of the pharmaceutical formulation to be aerosolizable.

The non-circular cross section **170** of the chamber **110** may take other forms. For example, as shown in Figure 3A, the non-circular cross section may be provided by a single projection **175**, or alternatively by more than two projections **175**, such as the six projections **175** shown in the version of Figure 3B. In the version of Figure 3B, there are an equal number of projections **175** as there are inlets **115**. Alternatively to the versions of Figures 2A, 2B, 3A and 3B, the projections **175** may be replaced with indentations that extend inwardly into the sidewalls **165**. In another version, such as shown in Figure 3C, 3D, and 3E, the chamber **110** may have a non-circular cross section **170** that is in the form of a polygon **180**, such as a square, hexagon or octagon. The sides of the polygon cause the bouncing and/or jarring of the receptacle **125**. In other version, such as those shown in Figures 3F, 3G, and 3H, the non-circular cross section **170** is more gently shaped. For example, the non-circular cross section may be oval **185** or rounded with multiple lobes **190**. These versions are also sufficient to increase the aerosolization of the pharmaceutical formulation.

The orientation of the chamber **110** may take one of several forms with its sidewalls about which the receptacle **125** moves being non-circular in cross section. For example, this non-circular cross section **170** may be along a plane that is orthogonal to an inhalation direction and/or orthogonal to an airflow direction as the air flows through the openings **120**. In one version, such as the version shown in Figures 1A through 1C, the chamber **110** is elongated with its longitudinal axis lying generally parallel to the inhalation direction **160**. In such an arrangement, the receptacle **125** is insertable lengthwise into the chamber **110** so that the capsule's longitudinal axis may be parallel to the longitudinal axis of the chamber **110**. In the version of Figures 1A through 1C, the chamber **110** is sized to receive a receptacle **125** containing a pharmaceutical formulation in a

manner which allows the capsule to move within the chamber **110** so that the receptacle **125** may rotate within the chamber **110** in a manner where the longitudinal axis of the receptacle **125** remains at an angle less than 80 degrees, and preferably less than 45 degrees, from the longitudinal axis of the chamber **110**. The movement of the receptacle **125** in the chamber **110** may be caused by the width of the chamber **110** being less than the length of the receptacle **125**.

A version of an aerosolization apparatus **100** comprising a chamber **110** having a non-circular cross section **170** is shown in Figures 4A through 4E. In this version, the housing **105** of the aerosolization apparatus **100** comprises a body **205** and a removable endpiece **210**. The endpiece **210** may be removed from the body **205** to insert a receptacle **125** in the chamber **110** which is formed when the body **205** and the endpiece **210** are connected together. The endpiece **210** comprises a partition **150** that is dome-shaped **215** and that blocks the forward end of the chamber **110**, and the partition **215** has the one or more outlets **120** extending therethrough. An example of an aerosolization apparatus with a partition **150** and chamber configuration are described in U.S. Patent 4,069,819 and in U.S. Patent 4,995,385, both of which are incorporated herein by reference in their entireties. As disclosed in U.S. Patent 4,995,385, the dome may comprise one or more protrusions extending into the chamber so that the capsule may contact the protrusions in a way that does not block any of the openings in the dome-shaped **215** partition **150**. The inlets **115** comprise a plurality of tangentially oriented slots **220**. When a user inhales **160** through the endpiece **210**, outside air is caused to flow through the tangential slots **220** as shown by arrows **225** in Figure 4E. This airflow **225** creates a swirling airflow within the chamber **110**. The swirling airflow causes the receptacle **125** to contact the partition **150** and then to move within the chamber **110** in a manner that causes the pharmaceutical formulation to exit the receptacle **125** and become entrained within the swirling airflow. In one specific version, the chamber **110** comprises a tapered section **230** that terminates at an edge **235**. During the flow of swirling air in the chamber **110**, the forward end of the receptacle **125** contacts and rests on the partition **150** and a sidewall of the receptacle **125** contacts the edge **235** and slides and/or rotates along the edge **235**. This motion of the capsule is particularly effective in forcing a large amount of the pharmaceutical formulation through one or more openings **130** in the rear of the receptacle **125**. Accordingly, in this version, the non-circular cross section **170** may be provided only on the edge **235** since the edge **235** is the portion of the sidewall **165** that contacts the receptacle **125** in use.

The one or more openings **130** in the rear of the receptacle **125** in the version of Figures 4A through 4E are created by a puncturing mechanism **250** that is slidable within the body **205**. The puncturing mechanism **250**, shown in its rest position in Figure 4A, comprises a plunger **255** attached at its forward end **260** to a puncture member **265**, which in the version shown is a U-shaped staple **270** having two sharpened tips **275**. The puncturing mechanism **250** further comprises a seating member **280** which contacts the plunger **255** and/or the puncture member **265** and is slidable relative to the plunger **255** and the puncture member **265**. To create the openings **130** in the receptacle **125**, the user applies a force **285** to the plunger **255**, as shown in Figure 4B, such as by pressing against an end surface **290** of the plunger **255** with the user's finger or thumb. The force **285** causes the plunger to slide within the body **205**. A slight frictional contact between the plunger **255** the a rear section **295** of the seating member **280** causes the seating member **280** to also slide within the body **205** until a forward seating surface **300** of the seating member **280** contacts the receptacle **125**, as shown in Figure 4B. The forward seating surface **300**, which may be shaped to generally match the shape of the receptacle **125**, secures the receptacle **125** between the seating member **280** and the partition **150**. The continued application of force **285** causes the plunger **255** and the puncture member **265** to slide relative to the seating member **280**, as shown in Figure 4C, to advance the puncture member **135** through openings **305** in the forward seating surface **300** and into the receptacle **125**. Upon the removal of the force **285**, a spring **310** or other biasing member urges the puncturing mechanism **250** back to its rest position. For example, the spring **310** may contact a shoulder **315** in the body **205** and press a flange **320** on the plunger **255** toward a rim **325** in the body **205**. The frictional engagement between the plunger **355** and the seating member **280** also returns the seating member **280** to its retracted position when the plunger is returned to its retracted position.

In one version, the receptacle **125** comprises a capsule. The capsule may be of a suitable shape, size, and material to contain the pharmaceutical formulation and to provide the pharmaceutical formulation in a usable condition. For example, the capsule may comprise a wall which comprises a material that does not adversely react with the pharmaceutical formulation. In addition, the wall may comprise a material that allows the capsule to be opened to allow the pharmaceutical formulation to be aerosolized. In one version, the wall comprises one or more of

gelatin, hydroxypropyl methylcellulose (HPMC), polyethyleneglycol-compounded HPMC, hydroxyproplycellulose, agar, or the like. Alternatively or additionally, the capsule wall may comprise a polymeric material, such as polyvinyl chloride (PVC). In one version, the capsule may comprise telescopically ajoined sections, as described for example in U.S. Patent 4,247,066 which is incorporated herein by reference in its entirety. The interior of the capsule may be filled with a suitable amount of the pharmaceutical formulation, and the size of the capsule may be selected to adequately contain a desired amount of the pharmaceutical formulation. The sizes generally range from size 5 to size 000 with the outer diameters ranging from about 4.91 mm to 9.97 mm, the heights ranging from about 11.10 mm to about 26.14 mm, and the volumes ranging from about 0.13 ml to about 1.37 ml, respectively. Suitable capsules are available commercially from, for example, Shionogi Qualicaps Co. in Nara, Japan and Capsugel in Greenwood, South Carolina. After filling, a top portion may be placed over the bottom portion to form the a capsule shape and to contain the powder within the capsule, as described in U.S. Patent 4,846,876, U.S. Patent 6,357,490, and in the PCT application WO 00/07572 published on February 17, 2000, all of which are incorporated herein by reference in their entireties.

In another version, the aerosolization apparatus **100** may be configured differently than as shown in Figures 1A through 1C and 4A through 4E. For example, the chamber **100** may be sized and shaped to receive the receptacle **125** so that the receptacle **125** is orthogonal to the inhalation direction, as described in U.S. Patent 3,991,761. As also described in U.S. Patent 3,991,761, the puncturing mechanism **250** may puncture both ends of the receptacle **125**. In such version, the non-circular cross-section may be provided along a sidewall that contacts the ends of the capsule. In another version, the chamber may receive the receptacle in a manner where air flows through the receptacle as described for example in U.S. Patent 4,338,931 and in U.S. Patent 5,619,985. In another version, the aerosolization of the pharmaceutical formulation may be accomplished by pressurized gas flowing through the inlets, as described for example in US Patent 5,458,135, U.S. Patent 5,785,049, and U.S. Patent 6,257,233, or propellant, as described in PCT Publication WO 00/72904 and U.S, Patent 4,114,615. All of the above references being incorporated herein by reference in their entireties.

In a preferred version, the invention provides a system and method for aerosolizing a pharmaceutical formulation and delivering the pharmaceutical formulation to the respiratory tract of the user, and in particular to the lungs of the user. The pharmaceutical formulation may comprise powdered medicaments, liquid solutions or suspensions, and the like, and may include an active agent.

The active agent described herein includes an agent, drug, compound, composition of matter or mixture thereof which provides some pharmacologic, often beneficial, effect. This includes foods, food supplements, nutrients, drugs, vaccines, vitamins, and other beneficial agents. As used herein, the terms further include any physiologically or pharmacologically active substance that produces a localized or systemic effect in a patient. An active agent for incorporation in the pharmaceutical formulation described herein may be an inorganic or an organic compound, including, without limitation, drugs which act on: the peripheral nerves, adrenergic receptors, cholinergic receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulatory system, synoptic sites, neuroeffector junctional sites, endocrine and hormone systems, the immunological system, the reproductive system, the skeletal system, autacoid systems, the alimentary and excretory systems, the histamine system, and the central nervous system. Suitable active agents may be selected from, for example, hypnotics and sedatives, psychic energizers, tranquilizers, respiratory drugs, anticonvulsants, muscle relaxants, antiparkinson agents (dopamine antagnonists), analgesics, anti-inflammatories, antianxiety drugs (anxiolytics), appetite suppressants, antimigraine agents, muscle contractants, anti-infectives (antibiotics, antivirals, antifungals, vaccines) antiarthritics, antimalarials, antiemetics, anepileptics, bronchodilators, cytokines, growth factors, anti-cancer agents, antithrombotic agents, antihypertensives, cardiovascular drugs, antiarrhythmics, antioxicants, anti-asthma agents, hormonal agents including contraceptives, sympathomimetics, diuretics, lipid regulating agents, antiandrogenic agents, antiparasitics, anticoagulants, neoplastics, antineoplastics, hypoglycemics, nutritional agents and supplements, growth supplements, antienteritis agents, vaccines, antibodies, diagnostic agents, and contrasting agents. The active agent, when administered by inhalation, may act locally or systemically.

The active agent may fall into one of a number of structural classes, including but

not limited to small molecules, peptides, polypeptides, proteins, polysaccharides, steroids, proteins capable of eliciting physiological effects, nucleotides, oligonucleotides, polynucleotides, fats, electrolytes, and the like.

Examples of active agents suitable for use in this invention include but are not limited to one or more of calcitonin, amphotericin B, erythropoietin (EPO), Factor VIII, Factor IX, ceredase, cerezyme, cyclosporin, granulocyte colony stimulating factor (GCSF), thrombopoietin (TPO), alpha-1 proteinase inhibitor, elcatonin, granulocyte macrophage colony stimulating factor (GMCSF), growth hormone, human growth hormone (HGH), growth hormone releasing hormone (GHRH), heparin, low molecular weight heparin (LMWH), interferon alpha, interferon beta, interferon gamma, interleukin-1 receptor, interleukin-2, interleukin-1 receptor antagonist, interleukin-3, interleukin-4, interleukin-6, luteinizing hormone releasing hormone (LHRH), factor IX, insulin, pro-insulin, insulin analogues (e.g., mono-acylated insulin as described in U.S. Patent No. 5,922,675, which is incorporated herein by reference in its entirety), amylin, C-peptide, somatostatin, somatostatin analogs including octreotide, vasopressin, follicle stimulating hormone (FSH), insulin-like growth factor (IGF), insulintropin, macrophage colony stimulating factor (M-CSF), nerve growth factor (NGF), tissue growth factors, keratinocyte growth factor (KGF), glial growth factor (GGF), tumor necrosis factor (TNF), endothelial growth factors, parathyroid hormone (PTH), glucagon-like peptide thymosin alpha 1, IIb/IIIa inhibitor, alpha-1 antitrypsin, phosphodiesterase (PDE) compounds, VLA-4 inhibitors, bisphosponates, respiratory syncytial virus antibody, cystic fibrosis transmembrane regulator (CFTR) gene, deoxyreibonuclease (Dnase), bactericidal/permeability increasing protein (BPI), anti-CMV antibody, 13-cis retinoic acid, macrolides such as erythromycin, oleandomycin, troleandomycin, roxithromycin, clarithromycin, davercin, azithromycin, flurithromycin, dirithromycin, josamycin, spiromycin, midecamycin, leucomycin, miocamycin, rokitamycin, andazithromycin, and swinolide A; fluoroquinolones such as ciprofloxacin, ofloxacin, levofloxacin, trovafloxacin, alatrofloxacin, moxifloxicin, norfloxacin, enoxacin, grepafloxacin, gatifloxacin, lomefloxacin, sparfloxacin, temafloxacin, pefloxacin, amifloxacin, fleroxacin, tosufloxacin, prulifloxacin, irloxacin, pazufloxacin, clinafloxacin, and sitafloxacin, aminoglycosides such as gentamicin, netilmicin, paramecin, tobramycin, amikacin, kanamycin, neomycin, and streptomycin, vancomycin, teicoplanin, rampolanin, mideplanin, colistin, daptomycin, gramicidin, colistimethate, polymixins such as polymixin B, capreomycin,

bacitracin, penems; penicillins including penicllinase-sensitive agents like penicillin G, penicillin V, penicillinase-resistant agents like methicillin, oxacillin, cloxacillin, dicloxacillin, floxacillin, nafcillin; gram negative microorganism active agents like ampicillin, amoxicillin, and hetacillin, cillin, and galampicillin; antipseudomonal penicillins like carbenicillin, ticarcillin, azlocillin, mezlocillin, and piperacillin; cephalosporins like cefpodoxime, cefprozil, ceftbuten, ceftizoxime, ceftriaxone, cephalothin, cephapirin, cephalexin, cephradrine, cefoxitin, cefamandole, cefazolin, cephaloridine, cefaclor, cefadroxil, cephaloglycin, cefuroxime, ceforanide, cefotaxime, cefatrizine, cephacetrile, cefepime, cefixime, cefonicid, cefoperazone, cefotetan, cefmetazole, ceftazidime, loracarbef, and moxalactam, monobactams like aztreonam; and carbapenems such as imipenem, meropenem, pentamidine isethiouate, albuterol sulfate, lidocaine, metaproterenol sulfate, beclomethasone diprepionate, triamcinolone acetamide, budesonide acetonide, fluticasone, ipratropium bromide, flunisolide, cromolyn sodium, ergotamine tartrate and where applicable, analogues, agonists, antagonists, inhibitors, and pharmaceutically acceptable salt forms of the above. In reference to peptides and proteins, the invention is intended to encompass synthetic, native, glycosylated, unglycosylated, pegylated forms, and biologically active fragments and analogs thereof.

Active agents for use in the invention further include nucleic acids, as bare nucleic acid molecules, vectors, associated viral particles, plasmid DNA or RNA or other nucleic acid constructions of a type suitable for transfection or transformation of cells, i.e., suitable for gene therapy including antisense. Further, an active agent may comprise live attenuated or killed viruses suitable for use as vaccines. Other useful drugs include those listed within the Physician's Desk Reference (most recent edition).

The amount of active agent in the pharmaceutical formulation will be that amount necessary to deliver a therapeutically effective amount of the active agent per unit dose to achieve the desired result. In practice, this will vary widely depending upon the particular agent, its activity, the severity of the condition to be treated, the patient population, dosing requirements, and the desired therapeutic effect. The composition will generally contain anywhere from about 1% by weight to about 99% by weight active agent, typically from about 2% to about 95% by weight active agent, and more typically from about 5% to 85% by weight active agent, and will also

depend upon the relative amounts of additives contained in the composition. The compositions of the invention are particularly useful for active agents that are delivered in doses of from 0.001 mg/day to 100 mg/day, preferably in doses from 0.01 mg/day to 75 mg/day, and more preferably in doses from 0.10 mg/day to 50 mg/day. It is to be understood that more than one active agent may be incorporated into the formulations described herein and that the use of the term "agent" in no way excludes the use of two or more such agents.

The pharmaceutical formulation may comprise a pharmaceutically acceptable excipient or carrier which may be taken into the lungs with no significant adverse toxicological effects to the subject, and particularly to the lungs of the subject. In addition to the active agent, a pharmaceutical formulation may optionally include one or more pharmaceutical excipients which are suitable for pulmonary administration. These excipients, if present, are generally present in the composition in amounts ranging from about 0.01 % to about 95% percent by weight, preferably from about 0.5 to about 80%, and more preferably from about 1 to about 60% by weight. Preferably, such excipients will, in part, serve to further improve the features of the active agent composition, for example by providing more efficient and reproducible delivery of the active agent, improving the handling characteristics of powders, such as flowability and consistency, and/or facilitating manufacturing and filling of unit dosage forms. In particular, excipient materials can often function to further improve the physical and chemical stability of the active agent, minimize the residual moisture content and hinder moisture uptake, and to enhance particle size, degree of aggregation, particle surface properties, such as rugosity, ease of inhalation, and the targeting of particles to the lung. One or more excipients may also be provided to serve as bulking agents when it is desired to reduce the concentration of active agent in the formulation.

Pharmaceutical excipients and additives useful in the present pharmaceutical formulation include but are not limited to amino acids, peptides, proteins, non-biological polymers, biological polymers, carbohydrates, such as sugars, derivatized sugars such as alditols, aldonic acids, esterified sugars, and sugar polymers, which may be present singly or in combination. Suitable excipients are those provided in WO 96/32096, which is incorporated herein by reference in its entirety. The excipient may have a glass transition temperatures (Tg) above about 35° C, preferably above about 40 °C, more preferably above 45° C, most preferably above about 55 °C.

Exemplary protein excipients include albumins such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, hemoglobin, and the like. Suitable amino acids (outside of the dileucyl-peptides of the invention), which may also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, tyrosine, tryptophan, and the like. Preferred are amino acids and polypeptides that function as dispersing agents. Amino acids falling into this category include hydrophobic amino acids such as leucine, valine, isoleucine, tryptophan, alanine, methionine, phenylalanine, tyrosine, histidine, and proline. Dispersibility- enhancing peptide excipients include dimers, trimers, tetramers, and pentamers comprising one or more hydrophobic amino acid components such as those described above.

Carbohydrate excipients suitable for use in the invention include, for example, monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), pyranosyl sorbitol, myoinositol and the like.

The pharmaceutical formulation may also include a buffer or a pH adjusting agent, typically a salt prepared from an organic acid or base. Representative buffers include organic acid salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid, Tris, tromethamine hydrochloride, or phosphate buffers.

The pharmaceutical formulation may also include polymeric excipients/additives, e.g., polyvinylpyrrolidones, derivatized celluloses such as hydroxymethylcellulose, hydroxyethylcellulose, and hydroxypropylmethylcellulose, Ficolls (a polymeric sugar), hydroxyethylstarch, dextrates (e.g., cyclodextrins, such as 2-hydroxypropyl-β-cyclodextrin and sulfobutylether-β-cyclodextrin), polyethylene glycols, and pectin.

The pharmaceutical formulation may further include flavoring agents, taste-masking agents, inorganic salts (for example sodium chloride), antimicrobial agents (for example

benzalkonium chloride), sweeteners, antioxidants, antistatic agents, surfactants (for example polysorbates such as "TWEEN 20" and "TWEEN 80"), sorbitan esters, lipids (for example phospholipids such as lecithin and other phosphatidylcholines, phosphatidylethanolamines), fatty acids and fatty esters, steroids (for example cholesterol), and chelating agents (for example EDTA, zinc and other such suitable cations). Other pharmaceutical excipients and/or additives suitable for use in the compositions according to the invention are listed in "Remington: The Science & Practice of Pharmacy", 19th ed., Williams & Williams, (1995), and in the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, NJ (1998), both of which are incorporated herein by reference in their entireties.

"Mass median diameter" or "MMD" is a measure of mean particle size, since the powders of the invention are generally polydisperse (i.e., consist of a range of particle sizes). MMD values as reported herein are determined by centrifugal sedimentation, although any number of commonly employed techniques can be used for measuring mean particle size. "Mass median aerodynamic diameter" or "MMAD" is a measure of the aerodynamic size of a dispersed particle. The aerodynamic diameter is used to describe an aerosolized powder in terms of its settling behavior, and is the diameter of a unit density sphere having the same settling velocity, generally in air, as the particle. The aerodynamic diameter encompasses particle shape, density and physical size of a particle. As used herein, MMAD refers to the midpoint or median of the aerodynamic particle size distribution of an aerosolized powder determined by cascade impaction.

In one version, the powdered formulation for use in the present invention includes a dry powder having a particle size selected to permit penetration into the alveoli of the lungs, that is, less than 20 μm mass median diameter (MMD), preferably less than 10 μm, more preferably less than 7.5 μm, and most preferably less than 5 μm, and usually being in the range of 0.1 μm to 5 μm in diameter. The delivered dose efficiency (DDE) of these powders may be greater than 30%, more preferably greater than 40%, more preferably greater than 50% and most preferably greater than 60% and the aerosol particle size distribution is about 1.0 - 5.0 μm mass median aerodynamic diameter (MMAD), usually 1.5 - 4.5 μm MMAD and preferably 1.5 - 4.0 μm MMAD. These dry powders generally have a moisture content below about 10% by weight, usually below about 5% by weight, and preferably below about 3% by weight. Such powders are described in WO 95/24183,

WO 96/32149, WO 99/16419, and WO 99/16422, all of which are all incorporated herein by reference in their entireties. Large, light particles also suitable for use in an aerosolization apparatus according to the invention are disclosed in U.S. Patents 5,874,064; 5,985,309; and 6,503,480, all of which are incorporated herein by reference in their entireties.

Although the present invention has been described in considerable detail with regard to certain preferred versions thereof, other versions are possible, and alterations, permutations and equivalents of the version shown will become apparent to those skilled in the art upon a reading of the specification and study of the drawings. For example, the cooperating components may be reversed or provided in additional or fewer number. Also, the various features of the versions herein can be combined in various ways to provide additional versions of the present invention. Furthermore, certain terminology has been used for the purposes of descriptive clarity, and not to limit the present invention. Therefore, any appended claims should not be limited to the description of the preferred versions contained herein and should include all such alterations, permutations, and equivalents as fall within the true spirit and scope of the present invention.